Gastric Pathology

Introduction

Gastric disease, gastric pathology, refers to inflammation of the stomach mucosa (gastro-itis, gastritis), the formation of ulcers through the mucosa, and cancer.

Gastritis can be separated into acute and chronic gastritis. Acute gastritis is caused by an imbalance of mucosal defense and acid production—either too much acid is secreted, or there are insufficient mucosal defenses. We will review the normal healthy mechanisms and how they may be tipped in acid's favor, causing acid damage to the mucosa or even deeper. Chronic gastritis is effectively one of two things: either infection with *H. pylori* or autoimmune gastritis.

Gastritis can range in severity based on how deep the damage reaches. When the mucosa is intact and only superficial inflammation is present, it is called gastritis. It is quite a distance from the lumen to the muscularis mucosae. The acid may have consumed the surface epithelium, but there is still lamina propria and the gastric pits and gastric glands to go. When the muscularis mucosae is still intact, the damage contained to the mucosa, it is called an erosion. If the damage reaches through the mucosa into the submucosa, that is an ulcer. If the damage goes through all layers of the stomach, that is a perforation.

This lesson covers acute gastritis, chronic gastritis, and peptic ulcer disease and its many etiologies, and closes with gastric adenocarcinoma.

Acute Gastritis

Acute gastritis is the disease of acute inflammation. Histologically, acute inflammation means neutrophils. Acute gastritis usually has an acute cause—toxin ingestion, NSAID overdose, stress-related mucosal injury—but many of the causes of acute gastritis are habits that occur over time. Thus there is an overlap between the causes of acute mucosal damage (acute gastritis) and the development of a chronic complication of chronic gastritis (such as an ulcer). So the mechanisms we're about to discuss, unless they are severe, can contribute to acute and chronic gastritis.

Numerous defenses protect the mucosa. Mucin is the primary component of mucus, a dense layer of which separates the lumen of the stomach from the epithelium. Below the mucus is the periciliary layer of bicarbonate-rich fluid. In addition, the epithelium contains tight junctions (zona adherens) that prevent anything that gets through the mucus and bicarbonate layers from reaching the lamina propria paracellularly. The bicarbonate used by the mucous cells comes from parietal cells. In the generation of H^+, carbonic anhydrase generates bicarbonate. That bicarbonate is exchanged for chloride in the microvasculature of the lamina propria. That bicarbonate is carried up to the surface, to the mucous cells. Thus, this "alkaline tide," as it is named, provides bicarbonate to the mucous cells at the same time that parietal cells are generating the acid that bicarbonate will defend against. But this is hard work, keeping the mucosa protected. An oxygen supply from the lamina propria is required to sustain the mucosal defenses. Worse, the surface cells are the furthest from the vascular supply. And because it is such hard work, the mucous cells die and need to be replaced. Thus, stem cells regenerate the surface mucous cells every 3–7 days. The **gastric acid**, **digestive enzymes**, and **mechanical trauma** constantly pound on the mucosa that makes them. In doing the work it is supposed to do, the mucosa puts itself at risk.

Humans then go and do something they aren't supposed to, and the mucosa starts to lose. A little damage—only a mild erosion—begets little symptoms. The whole gastric gland and surface epithelium is replaced in a week anyway. If the insult is removed, the mucosa will heal itself. The problem is that when the added insult is **severe** or **prolonged**, the mucosa loses and doesn't have a chance to rebuild. The major insults are NSAIDs, *H. pylori*, and ischemia. Other causes exist, but these are the ones to know.

NSAIDs and **aspirin** inhibit COX-2, which in turn eliminates protective prostaglandins, especially PGE_2 and PGI_2. ***H. pylori* infection** causes ongoing, chronic, acute inflammation. That is, there is an acute inflammatory reaction in the lamina propria (neutrophils), but the infection is present for a long time. **Alcohol** and **tobacco** are not independent risk factors for developing gastritis or ulceration but do add to the severe insults. **Ischemia** is thought to be the mechanism of stress ulcers—either splanchnic vasoconstriction or hypotension.

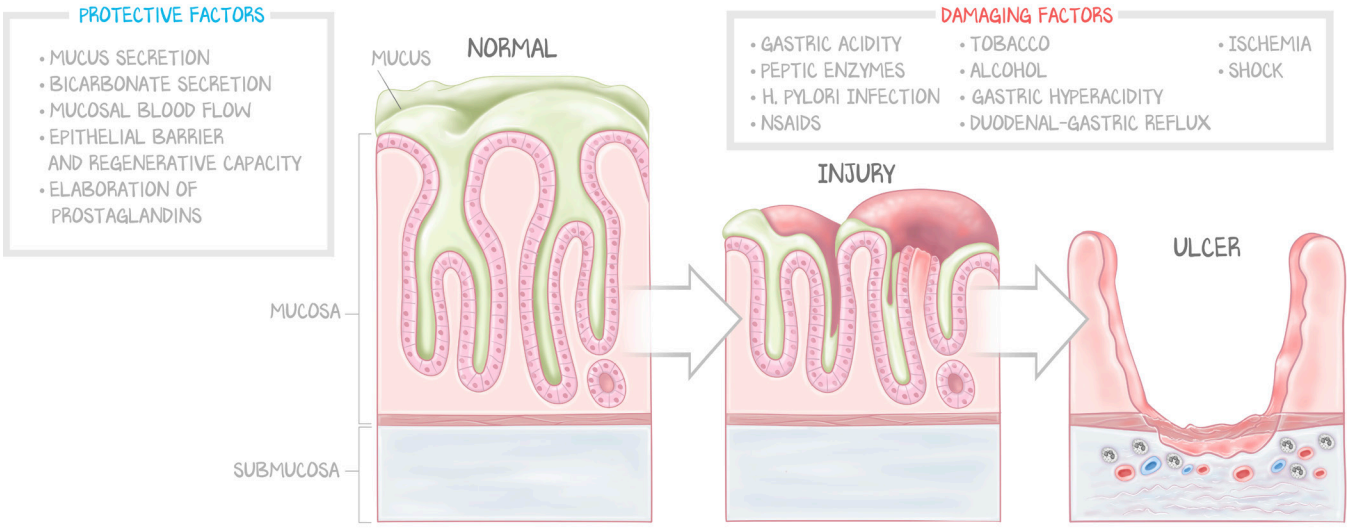

Figure 6.1: Mechanisms of Acute Gastritis
Injury can occur due to a loss of protective factors—caused by ischemia, shock, and NSAIDS—or an increase in gastric acid secretion—caused by alcohol, tobacco, H. pylori, and endocrinopathies that stimulate acid secretion. If injury is done to only the mucosa—epithelium and lamina propria—but stays above the muscularis mucosae, it is termed erosion. Ongoing injury, or severe injury at once, will progress to erosion into the submucosa, called ulceration.

Acute gastritis has multiple presentations because it has multiple etiologies. The presentation will likely follow the condition that causes the gastritis. In general, symptoms of gastritis are difficult to separate from those of dyspepsia and GERD. There may be burning retrosternal pain (inflammation), gnawing epigastric pain (ulcer), nausea, or vomiting. Acute gastritis is nonspecific, and its cause can never be deduced from its clinical symptoms.

Acute Ulcers

Peptic ulcer disease is a complication of chronic gastritis. Acute ulcers develop in severely ill patients, even without preexisting chronic gastritis. There are three named instances in which this occurs: stress ulcers, Curling ulcers, and Cushing ulcers. The unique features shared by each are that they are sharply demarcated from the normal surrounding mucosa, and they form rapidly in what would have been a normal stomach.

Stress ulcers is the generic term for the other unnamed ulcers ("shock, sepsis, and trauma") in which hypotension and ischemia definitely play a role. More than 75% of critically ill patients develop gastric lesions within the first 3 days of their illness. There was a time where all hospitalized patients got prophylactic PPIs to prevent stress ulcers. Now only very high-risk patients get prophylactic H_2 blockers. See GI: Digestion and Absorption: Start to Finish #5: *Physiology and Pharmacology of the Stomach* for details. What's more, the best prophylaxis is food. So, likely it is both the stress of the illness and the absence of food to digest that lead to the ulcers.

Cushing's ulcer is caused by an increase in **intracranial pressure**. The increased intracranial pressure causes Cushing's reflex, which presents with hypertension and bradycardia. It is thought that the cardioinhibitory reflex that leads to bradycardia (vagal discharge) may also lead to a disproportionate vagal discharge in the stomach and related cells, leading to increased acid production.

Curling ulcers occur in **burn patients** ("*a curling iron is hot*") and are associated with duodenal ulcers. The same pathogenesis is likely true for all patients with hypotension, although the phenomenon was classically described in burn patients. A patent blood supply is necessary for normal healing, to promote mucosal cells to be able to heal after acidic injury and to be able to secrete bicarbonate and mucus. Hypotension limits that ability.

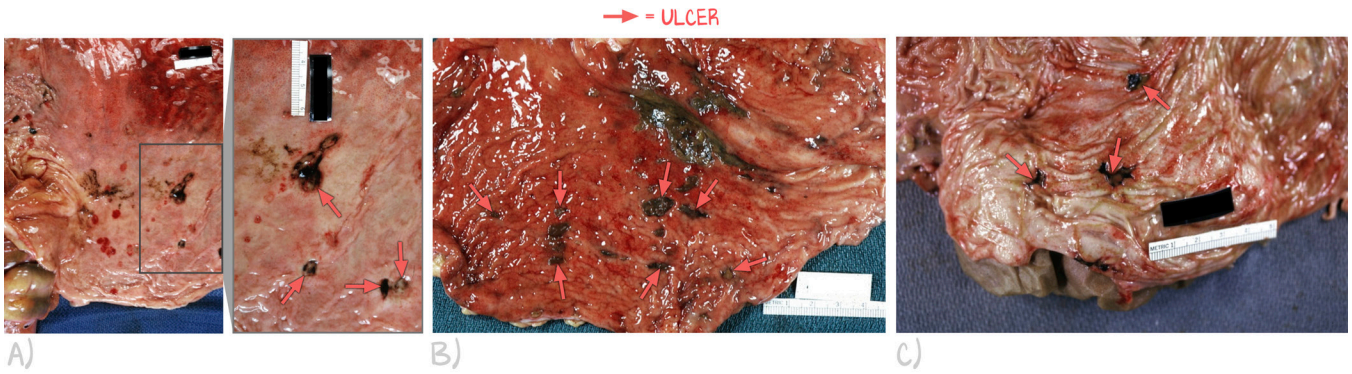

Figure 6.2: Stress Ulcers
Each example shows multiple, small, superficial ulcers of the gastric mucosa. They have no predilection for location and are distributed throughout the stomach (which is why there is no esophagus or duodenum for orientation in these images). Each ulcer has a sharp edge, with normal mucosa adjacent to a sharply demarcated lesion. The different samples show Curling ulcers, Cushing ulcers, and stress ulcers. The ulcers are indistinguishable, and the ulcer name depends on the clinical scenario, not the appearance of the ulcers in the stomach.

Chronic Gastritis

Chronic gastritis is long-term (chronic) stomach (gastro-) inflammation (-itis). Long-term inflammation generally results in **atrophy of the stomach mucosa**. There are two important types: autoimmune gastritis and infection with *H. pylori*. Autoimmune gastritis more commonly affects the body and fundus, so it has been named the "fundus type" chronic gastritis and has also been referred to as type A chronic gastritis. *H. pylori* infection causes similar atrophy of the mucosa but occurs in the antrum, so it has been named the "antral type" chronic gastritis and has also been referred to as type B chronic gastritis.

	H. PYLORI-ASSOCIATED	AUTOIMMUNE
LOCATION	**ANTRUM**	**BODY**
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to decreased	Increased
Serology	Antibodies against *H. pylori*	Antibodies against parietal cells (H^+/K^+-ATPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, MALToma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas	Autoimmune disease; thyroiditis, diabetes mellitus, Graves' disease

Table 6.1: Comparison Between *H. pylori*-Associated Gastritis and Autoimmune Gastritis

Chronic gastritis can progress to ulcers. The NSAIDs, *H. pylori*, alcohol, and tobacco that cause acute gastritis can also lead to the same complication in chronic gastritis—peptic ulcer disease. We'll cover autoimmune gastritis and *H. pylori* infection, then move into peptic ulcer disease.

Autoimmune Gastritis = Pernicious Anemia

Chronic autoimmune gastritis is caused by the antibody-mediated destruction of parietal cells (cytotoxic type II hypersensitivity). Antibodies are detectable in serum and are present in 80–90% of patients. Antibodies against H^+/K^+-ATPase (**proton pump antibodies**) and intrinsic factor (**intrinsic factor antibodies**) are useful in the detection of disease. Whether the antibodies are the main cause of disease is disputed, but the autoimmune reaction to parietal cells is systemic—anywhere there are parietal cells, an inflammatory infiltrate (lymphocytes and plasma cells) is found. This causes marked **mucosal atrophy** of the **body and fundus** (everywhere fundic glands are), sparing the cardia and antrum (everywhere fundic glands are absent). This is in contrast to similar findings in *H. pylori*-induced atrophic changes, which tend to be punctate rather than universal. As the parietal cells are lost, so too are the fundic glands they reside in. Thus, in addition to the loss of parietal cells, chief cells are lost.

This autoimmune destruction of parietal cells leads to **impaired gastric acid secretion**, resulting in **achlorhydria** (low hydrochloric acid). This autoimmune destruction of parietal cells leads to **impaired intrinsic factor secretion**, resulting in **impaired B_{12} absorption**. This is the pathogenesis of pernicious anemia (we will discuss this more in Heme/Onc). B_{12} is absorbed in the terminal ileum and then only when bound to intrinsic factor. Without intrinsic factor, B_{12} cannot be absorbed, which results in megaloblastic macrocytic anemia and eventual subacute combined degeneration of the cord (loss of proprioception from impaired myelin synthesis).

Patients often have a coexisting autoimmune condition, such as Graves' disease (thyroid), Hashimoto's thyroiditis, myasthenia gravis, or Lambert-Eaton syndrome. Because the progression is slow and variable, the autoimmune destruction likely occurs over decades, with most patients being diagnosed in their 60s.

Chronic autoimmune gastritis causes gastric **intestinal metaplasia**. Metaplasia, inflammation, and proliferation are all risk factors for **gastric adenocarcinoma**. Loss of parietal cells means loss of acid secretion and, therefore, increased gastrin expression. This increased gastrin can lead to a carcinoid tumor in the pancreas.

H. pylori

***H. pylori* chronic gastritis** is caused by an infection with *H. pylori*. It is the most common cause of gastritis. It was the most common cause of ulcers until it was identified. Now, the worldwide incidence of *H. pylori* and peptic ulcers has decreased due to antibiotic treatment. *H. pylori* live **within the mucus layer** and secrete **urease,** which cleaves urea, offering its own buffer against gastric acid. It lives best in the antrum, where no acid is produced, so antral biopsies are preferred when diagnosing the condition. *H. pylori* also have two **cytotoxic proteins** that damage the epithelial layer of the stomach.

The diagnosis is confirmed with an endoscopy with biopsy showing **motile, gram-negative rods** in the gastric mucosa. Other testing methods exist (see the table below). You should not be asked about management decisions at this stage of your training. However, in general, if an infection is found through any mechanism, the steps should be to treat with triple therapy, then confirm eradication with stool antigen testing.

TESTING	WHAT IT SHOWS YOU	ACTIONS
Serum IgG	Previous infection	If never treated, treat
Urea breath test	Suspect current infection	If positive, treat
Stool antigen	Confirm eradication	Obtain after treatment
Biopsy	Organisms or not	If positive, treat

Table 6.2: *H. pylori* Testing
Tests, what they are good for, and what your reaction should be to a positive test.

TRIPLE THERAPY	QUADRUPLE THERAPY
Amoxicillin (Metronidazole if PCN-allergic)	Bismuth
Clarithromycin	Tetracycline
Proton pump inhibitor	Proton pump inhibitor
	Metronidazole

Table 6.3: *H. pylori* Treatment
Triple therapy is more practically efficacious. If triple therapy fails, choose quadruple therapy. If the patient is allergic to penicillin, you can do triple therapy with metronidazole instead.

H. pylori are sneaky. The immune system knows there is an infection. The superficial lamina propria contains many plasma cells. Neutrophils try to get to the *H. pylori*, directed by antibodies made by those plasma cells. But they can't get to it. Trying to results in neutrophils exiting the mucosa into gastric glands, effectively causing abscesses (lots of neutrophils, but no bacteria). This results in intraepithelial neutrophils—almost as if the neutrophils are stretching out as far as they can to get at the bacteria, but the bacteria are in the mucus layer, and the neutrophils can't get to them. Unless treated with antibiotics, the *H. pylori* antigens persist, and an angry immune system revs up to fight the bacteria. Lymphoid aggregates, some with germinal centers, are frequently present in the lamina propria. This thickens the lamina propria and gives the appearance of thickened rugae. Thus, **intraepithelial neutrophils** and **subepithelial plasma cells** (in the lamina propria) are the hallmarks of *H. pylori* gastritis.

H. pylori live best in the antrum, where there is no acid being secreted. Over time, the infection can advance to involve the body or fundus. When it does, the mucosa becomes atrophic, with the loss of parietal cells and chief cells, turning the affected mucosa of the body into mucosa like that of the antrum. In contrast to autoimmune gastritis, this is patchy rather than diffuse. The ongoing activation of lymphocytes predisposes the patient to **MALToma**. Atrophy results in intestinal metaplasia, which, like in autoimmune gastritis, is a risk factor for malignant transformation into **adenocarcinoma**. Treating *H. pylori* with antibiotics prevents both.

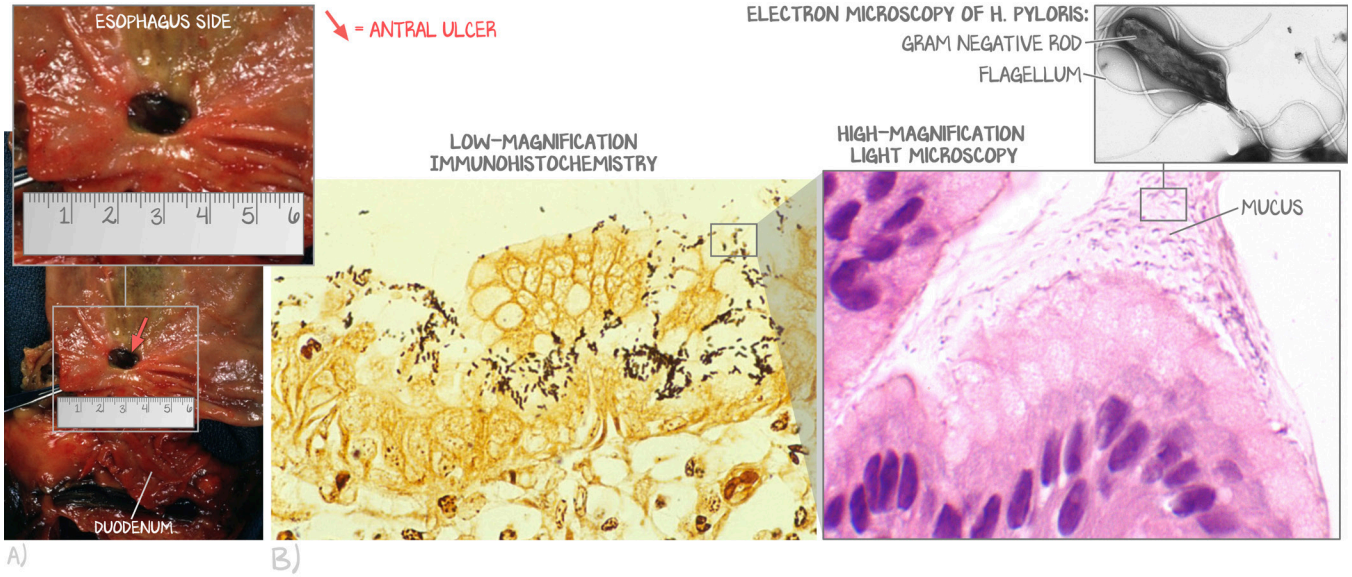

Figure 6.3: *H. pylori* Peptic Ulcers
H. pylori ulcers are often found in the antrum, where the antral glands secrete only mucus, rather than in the corpus or fundus, where the fundic glands secrete acid. *H. pylori* can be identified by immunohistochemical staining (dark dots that line a poorly staining mucosa), barely visualized on high-powered H&E stain, and clearly visualized by electron microscopy. *H. pylori* is a flagellated, gram-negative spiral-shaped rod.

Peptic Ulcer Disease

Peptic ulcer disease is a complication of chronic gastritis. There are three levels of severity: erosions are damage to the mucosa, ulcerations reach through it into the submucosa, and perforations reach through the muscularis externa and associated connective tissue, thereby either opening into the peritoneal cavity or forming a fistula to a nearby organ.

In clinical practice, you are not able to deduce the location of an ulcer based on the presenting symptoms. If an ulcer is suspected, an endoscopy is done. When endoscopy is done, certain features of the ulcer are suggestive of the etiology, but none is pathognomonic. A biopsy is performed to determine the etiology, specifically to rule out *H. pylori* and cancer. Ulcers can occur anywhere, and their location does not dictate their complication. However, licensure examinations continue to test learners' ability to relate the symptoms to the timing of food and the appearance on endoscopy and to know the relationship between the location of the ulcer and the possible consequences. It isn't to say that a keen clinician cannot anticipate the finding before the endoscopy or biopsy; some may have that skill. It is to say that because that anticipation does not change management, it is faulty to teach this. But the teaching is perpetuated so aggressively that we yield and will teach it as well. Food's effects on pain, the location of ulcers, their number and appearance, etc.—all of it is associative only, not pathognomonic.

There are two main types of peptic ulcers: gastric and duodenal. For a licensing exam, you are most likely going to get a history, and will have to determine whether it is gastric (hurts with food) or duodenal (hurts 1–3 hours after food). Regardless of your anticipated findings, endoscopy is done, biopsies are taken, **proton pump inhibitors** are prescribed, and modification of risk factors is recommended (no alcohol, tobacco, or NSAIDs). Ulcers can erode into vessels, presenting with an acute GI bleed. Ulcers can **penetrate the wall**, forming **fistulas** with nearby organs or **perforating** into the peritoneal cavity. Perforation is shown as **air under the diaphragm**. Ulcers may also be a malignancy, and so all ulcers should be biopsied. Most ulcers hurt. Some ulcers bleed. All ulcers need to be treated.

Gastric ulcers. In gastric ulcers, there is gnawing **epigastric pain** that **worsens before and during meals**. The cephalic and gastric phases are when acid is secreted. Initially, no chyme is allowed into the duodenum. Gastric ulcers are exposed to the acid, and so burn. Burning hurts. Gastric ulcers are typically found in the lesser curve of the antrum. About 75% of these are associated with *H. pylori* and are thought to be primarily a **decreased mucosal barrier** problem. The etiology will adjust the endoscopic findings. NSAID ulcers are multiple and small. Malignancy is associated with **heaped-up margins**. *H. pylori* and other forms will be larger, singular, and **punched-out** with clean, well-defined margins.

BOARD TEST POINT	LOCATION	ASSOCIATION
Gastric ulcer bleeding	Lesser curvature	Left gastric artery
Duodenal ulcer bleeding	Posterior duodenal wall	Gastroduodenal artery
Perforation	Anterior ulcers	Air under diaphragm

Table 6.4: High-Yield Testing Points on Licensure Exams

Duodenal ulcers are more common than gastric ulcers (duodenal, 0.58 per 1000 patient-years; gastric, 0.21 per 1000 patient-years). There is a near **100% association with *H. pylori*** (*H. pylori* causes duodenal ulcers), although duodenal ulcers can also be seen with gastrinoma, which comes with a significantly elevated acid production, known by the eponym Zollinger-Ellison syndrome. They are caused by the inability of the duodenum to neutralize stomach acid. Because the acid is greatest at the entry point, the **proximal duodenum** is most often involved, usually on the anterior wall. This will likely perforate and show air under the diaphragm. There is **gnawing epigastric pain** that comes on **hours after eating** and is **relieved by eating**. The biopsy will show the hypertrophy of Brunner's glands.

Zollinger-Ellison syndrome is caused by an endocrine tumor of the **pancreas** that autonomously secretes gastrin (gastrinoma). Gastrin levels rise to over a hundred times normal levels; a gastrin level > 1,000 is diagnostic of Zollinger-Ellison. This causes significant overproduction of gastric acid, leading to multiple large ulcers. If there are large ulcers on endoscopy, especially if they are **multiple** and in the **duodenum**, consider Zollinger-Ellison. Gastrin is also a trophic signal for chief and parietal cells, so Zollinger-Ellison causes hypertrophy of the stomach fundus and body. This upregulated proliferation puts the patient at risk for gastric adenocarcinoma. Zollinger-Ellison is a tumor of the pancreas that does NOT turn malignant, but Zollinger-Ellison causes gastric adenocarcinoma. Secretin, a hormone that normally inhibits G cells, causes a paradoxical increase in the already elevated gastrin and is the laboratory test of choice for diagnosis.

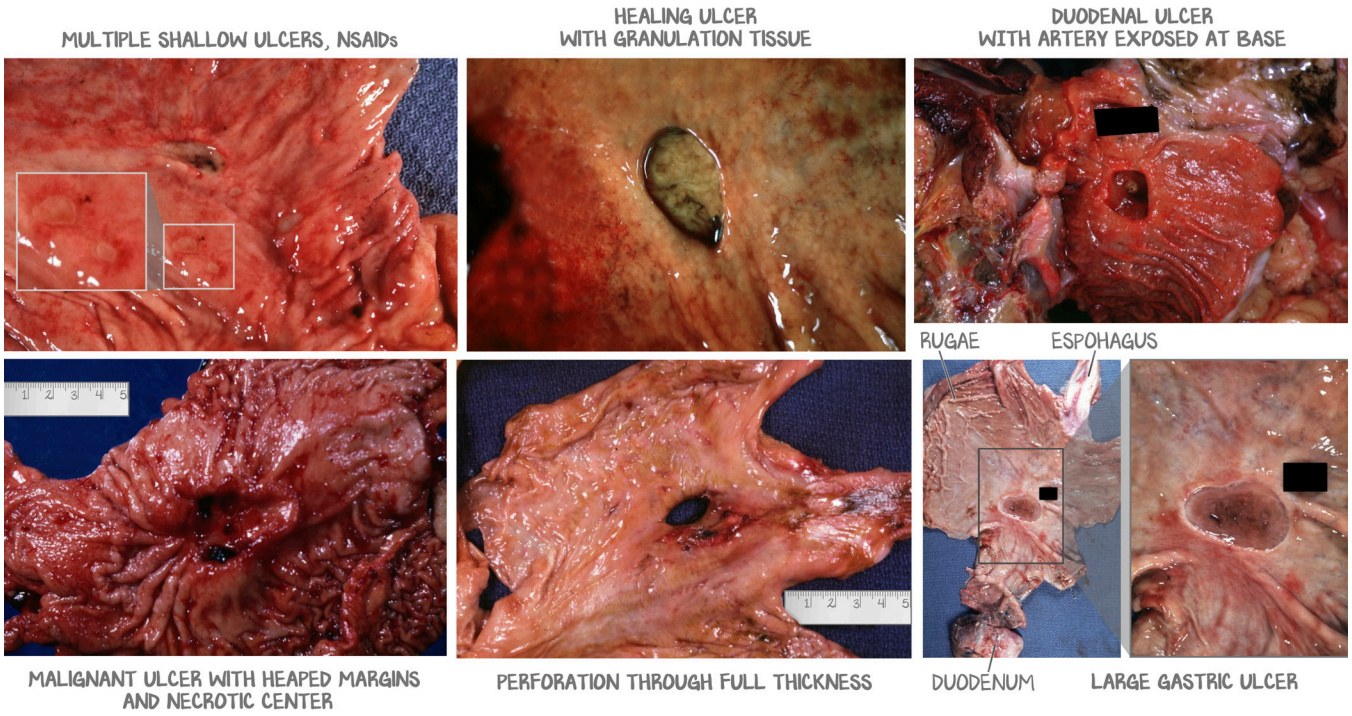

Figure 6.4: Ulcers
A variety of gastric ulcers, including multiple shallow ulcers caused by NSAIDs, a healing ulcer, a duodenal ulcer with an exposed artery at the base, a heaped-up necrotic ulcer due to gastric cancer, a perforated ulcer, and a large gastric ulcer.

Gastric Adenocarcinoma

The incidence of stomach cancer has plummeted since the identification and treatment of *H. pylori*, down almost 90%. However, there are still sporadic mutations and environmental irritants (nitrosamines) that cause stomach cancer. Unfortunately, it is usually diagnosed late, by which time the cancer has already **metastasized**. Gastric adenocarcinoma metastasizes to sites that would be unusual for other cancers. Gastric adenocarcinoma metastasizes to a supraclavicular lymph node (**Virchow's node)**, periumbilical lymph nodes (Sister Mary Joseph's nodule), left axillary lymph node (Irish node), the **ovaries** (called a **Krukenberg tumor**), or the pouch of Douglas (Blumer's shelf). Because there is so much space in the abdomen, clinical detection is difficult before metastasis. The symptoms are those of chronic gastritis: dyspepsia, burning epigastric pain, and, if an ulcer develops, gnawing epigastric pain that changes with food. By the time weight loss, anorexia, and **early satiety** are felt, the tumor has progressed well beyond curable stages.

Nitrosamine ingestion and ***H. pylori*** are known as the two major contributing pathologies. Pernicious anemia is associated with increased risk, but that is not a common condition. Nitrosamines were a popular way of preparing and storing food in Japan, which is why the incidence was so high there. To be clear, this is not a genetic predisposition but rather an environmental exposure. Being of Japanese descent does not increase the risk of gastric adenocarcinoma, and non-native individuals who lived in Japan during the use of nitrosamines have the same risk as native Japanese. Screening endoscopies are still being performed in Japan, but the cessation of using nitrosamines has caused a decline in cancers. Such screening is not as useful in places like the US and Europe, which have lower rates of adenocarcinoma and use significantly less nitrosamines than Japan. Remarkably, even though the two progress in wildly different fashions, both the intestinal and diffuse types demonstrate mutations in two overlapping pathways. The loss of E-cadherin in the diffuse type (leading to upregulation of β-catenin) and the loss of APC in the intestinal type (leading to an upregulation of β-catenin) seem to be the leading mutations. This implies that although there are two morphologic presentations (discussed next), it appears that both share similar genetics.

Intestinal type gastric cancer. This occurs in the anterior antrum, along the lesser curvature of the stomach. This is the same place we found *H. pylori* ulcers, but these are not necessarily caused by *H. pylori* infections. The chronic progressive inflammation results in **intestinal metaplasia** (thus the intestinal type). The intestinal type will present with **intestinal epithelium**, so it will show glands, much like the duodenal villi and their simple columnar epithelium rich in mucin-secreting goblet cells. These are bulky tumors that form ulcers.

Diffuse type adenocarcinoma demonstrates no glands, but instead **poorly differentiated cells** with **signet-ring cells**. These cells do not form glands but instead have large mucin vacuoles that expand the cytoplasm and push the nucleus to the periphery, creating big ol' pink circles capped by a nucleus (like a signet ring as seen from the side). Signet rings were those big rings with the family crest on them that were used to sign letters with wax. One of the key features in the pathogenesis is the loss of regulation of E-cadherin, so cells often permeate the mucosa and stomach wall individually or in small clusters (not forming glands, but acting on their own). The gross appearance is unique in that there is **linitis plastica**, a thickening of the mucosal layer of the stomach, and the loss of rugal folds. This is also called a **desmoplastic reaction**.

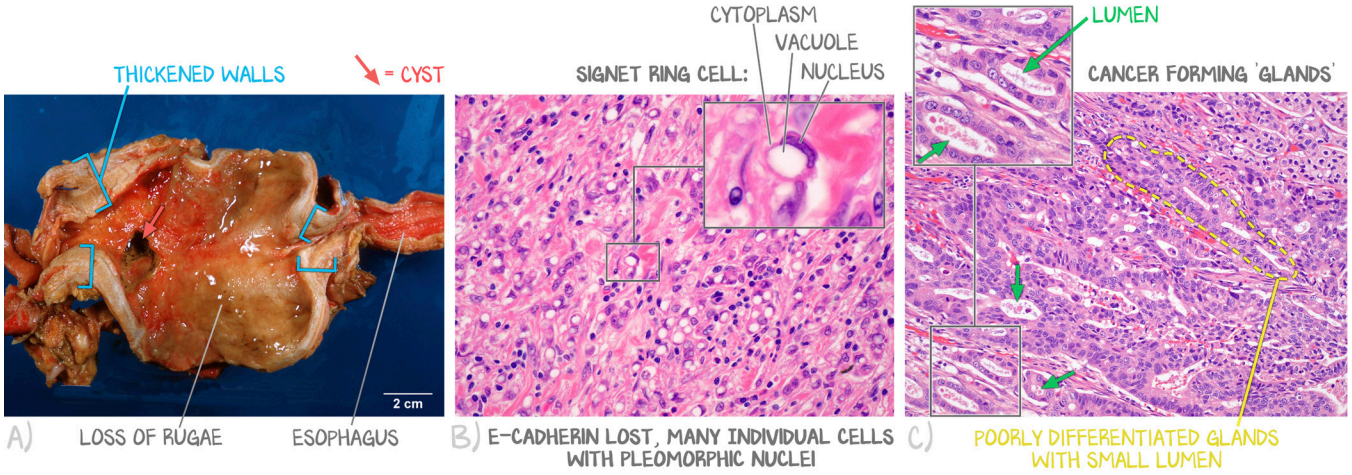

Figure 6.5: Gastric Cancer
(a) Linitis plastica is one variant of gross appearance in gastric cancer (the malignant ulcer in Figure 6.4 is the other). Linitis plastica involves the thickening of the stomach wall and the loss of rugae. This is usually seen in diffusely infiltrating gastric cancer, sometimes called signet ring gastric cancer. (b) Due to the loss of E-cadherin, the protein that holds epithelial cells together, diffusely infiltrating gastric cancer demonstrates individual cells within the underlying stroma—they aren't oriented the same way, and they don't form glands or ducts. Signet ring cells classically have white, vacuolated (puffy) cytoplasm with off-center nuclei (purple), giving them the appearance of a signet ring. (c) Cuboid and columnar cells poorly form glands.

Honorable Mention

You'll see *H. pylori* again in Heme/Onc. *H. pylori* do increase the risk of both types of gastric adenocarcinoma. *H. pylori* also cause chronic inflammation that promotes lymphocyte proliferation and germinal center formation. That leads to a lymphoma of the GI tract, a mucosa-associated lymphoid tissue (MALT) tumor, or MALToma. Treating *H. pylori* prevents not only gastric adenocarcinoma but also lymphoma. *H. pylori* . . . one bad bug.

Citation

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